REMARKS

Applicants acknowledge receipt of an Advisory Action dated January 28, 2003. A request for a Continued Prosecution Application ("CPA") is being filed is being filed concurrently herewith. The Examiner is requested to consider the foregoing amendments and following remarks in the newly established CPA. In this response Applicants have amended claim 1 to incorporate the subject matter of claim 7 and intervening claims 4 and 5. Accordingly, claims 4, 5 and 7 have been cancelled without prejudice or disclaimer. Following entry of these amendments, claims 1-3, 6, 8-11, 15-21, 23, 24 and 27-32 are pending in the application. The Examiner has withdrawn claims 19-21, 27 and 32 from consideration as being drawn to non-elected subject matter.

Reconsideration of the present application is respectfully requested in view of the foregoing amendments and the remarks which follow.

Notice of Abandonment

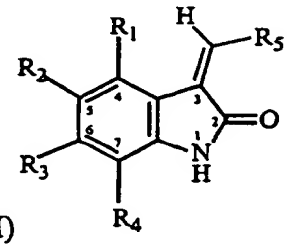
As an initial matter, Applicants note that the Examiner erroneously issued a Notice of Abandonment on February 26, 2003. Applicants filed a petition to revive on March 19, 2003 (copy enclosed) establishing *inter alia* that a Notice of Appeal was timely filed on November 21, 2003. Accordingly, Applicants submit that this response is being properly filed with a petition for a 3 month extension of time.

Rejections Under 35 U.S.C. §112, 1st Paragraph

On page 2 of the Advisory Action, the Examiner has maintained the rejection of claims 1-3, 5-11, 16-18, 23-24 and 28-31 under 35 U.S.C. §112, 1st paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants respectfully traverse this rejection for the reasons set forth below.

As an initial matter, Applicants note that claim 1 has been amended *supra* to incorporate the subject matter of claims 4, 5 and 7. Thus, claim 1 now recites: "A method of determining an efficacious dose of a compound administered to a subject for the purpose of modulating angiogenesis, comprising the steps of:

(a) administering the compound to a patient, wherein the compound is a receptor antagonist that inhibits a receptor involved in angiogenesis and wherein the compound is an indolinone compound, having the structure set forth in formula I:



(I)

wherein

(i) R1, R2, R3, and R4 are selected from the group consisting of hydrogen, trihalomethyl, hydroxyl, amine, thioether, cyano, alkoxy, alkyl, amino, bromo, fluoro, chloro, iodo, mercapto, thio, cyanoamido, alkylthio, aryl, heteroaryl, carboxyl, ester, oxo, alkoxycarbonyl, alkenyl, alkoxy, nitro, alkoxyl, and amido moieties; and

(ii) R5, is an optionally substituted aryl or heteroaryl cyclic moiety;

or a pharmaceutically acceptable salt, ester, amide, prodrug, isomer, or metabolite thereof;

(b) monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL8, and t-PA;

(c) constructing a standard curve; and

(d) determining the efficacious dose based on the standard curve." (Emphasis added).

In the Final Office Action (dated May 21, 2002), the Examiner states that the specification, while being enabling for monitoring markers known in the art to correlate to angiogenesis for the purpose of determining an effective dose of an angiogenesis inhibitor, does not reasonably provide enablement for monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL-8, and t-PA, for the purpose of determining an effective dose of an angiogenesis modulator. On page 4 of the Final Office Action, the Examiner states that "the specification fails to provide any guidance or objective evidence that any of the markers which are taught or suggested by the specification in fact correlate to angiogenesis." The Examiner continues, on page 5 of the Final Office Action, arguing that "[t]he state of the art of drug dosage determination is complex and unpredictable, with many factors which complicate the effective determination of a dose" and concludes that "one skilled in the art would not be enabled to practice the invention commensurate in scope with the claims." Applicants submit that the Examiner has failed to establish a proper basis for rejection under 35 U.S.C. §112, 1st paragraph.

Applicants submit that the markers recited in present claim 1 (tissue factor, CD40, u-PA, ETS-1, IL-8, and t-PA) are enabled within the disclosure of the present application. The Examiner's attention is directed to information in the instant specification which provides enabling support for these markers. Specifically, the Examiner's attention is directed to the description on pages 23-26 of the specification, particularly the discussion under the heading "IV. Other Markers" on pages 24 and 25.

In the Advisory Action, the Examiner states that "a review of the cited support [from Applicants' response dated November 21, 2002] shows that the support is rife with uncertainties". Applicants respectfully disagree with the Examiner's statement. In response, Applicants direct the Examiner's attention to page 25, lines 15-16, where Applicants state that "[t]he foregoing enumerated a list of some of the possible markers that can be used with the techniques of the present invention." (Emphasis added). Thus, Applicants have expressly stated in the specification that the listed markers can be used in the presently claimed invention. As discussed *infra*, Applicants specification and the statements therein must be presumed enabled until the Examiner explains why she doubts the truth or accuracy of any statement in the disclosure.

On page 3 of the Advisory Action, the Examiner states that "[a]lthough Applicant cites support in the specification and cites case-law, it is noted that Applicant does not argue that the Examiner is incorrect in the finding that the invention is not enabled because the specification fails to provide any guidance or objective evidence that any of the markers which are taught or suggested by the specification in fact correlate with angiogenesis of that [*sic*] the state of the art is complex and unpredictable." Applicants respectfully disagree. So that it is unambiguously clear for the Examiner, Applicants expressly argue here that the Examiner is incorrect in the finding that the presently claimed invention is not enabled.

With regard to whether the claimed markers correlate to angiogenesis, Applicants respectfully disagree with the Examiner's position and submit that the Examiner has failed to come forward with objective evidence of non-enablement and has thereby improperly shifted her burden to Applicants.

As discussed *supra*, Applicants have stated, in the specification, that the claimed markers correlate to angiogenesis. It is well settled law that the Applicants' specification is considered presumptively accurate and enabling, absent contrary which must be presented by the Examiner. In re Wright, 27 USPQ2d 1510 (Fed Cir. 1993). Indeed, as stated by the court in In re Marzocchi,

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to trouble and expense of supporting his presumptively accurate disclosure.

439 F.2d at 223. Thus, Applicants enjoy a presumption of enablement, and a failure to rebut this presumption means that their specification is enabling as a matter of law.

The present Advisory Action, rather than recognizing Applicants' presumption, improperly shifts the burden to Applicants to positively prove enablement. Clearly, such a burden shift is not proper under the law. Absent a clear showing by the Examiner as to why these markers do not correlate with angiogenesis, Applicants specification is fully enabled.

Finally the Examiner's statement that "the art of drug dosage and determination is complex and unpredictable" is merely conclusory. Applicants contend that, in view of the foregoing, this argument of unpredictability is not sufficient to meet the requirement for a prima facie establishment of lack of enablement.

In Wands, the Federal Circuit indicated that

> [i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole.

Id., at 737, 740. Moreover, the critical inquiry is whether any experimentation is required is undue. The Examiner has not demonstrated that it would require undue experimentation to practice the claimed invention. "Enablement . . . is not precluded even if some experimentation is necessary." Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections under §112, 1st paragraph.

Rejections Under 35 U.S.C. §103

On page 3 of the Advisory Action, the Examiner has maintained 4 different rejections under 35 U.S.C. §103. Specifically:

- The Examiner has maintained the rejection of claims 1-6, 9-11, 15-18 and 23-24 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 6,177,401 to Ullrich *et al.* (hereafter "Ullrich") in view of U.S. Patent 5,942,385 to Hirth (hereafter "Hirth") in view of The Journal of Biological Chemistry, Vol. 270, No. 17, pages 9709-9716 (hereafter "Mandriota") and further in view of Fingl and Woodbury, The Pharmacological Basis of Therapeutics, Chapter 1, pages 25-33 (hereafter "Fingl and Woodbury").

- The Examiner has maintained the rejection of claims 1-11, 15-18, 23-24 and 28 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 5,792,783 to

Tang *et al.* (hereafter "Tang") in view of Hirth in view of Mandriota, and Fingl and Woodbury.

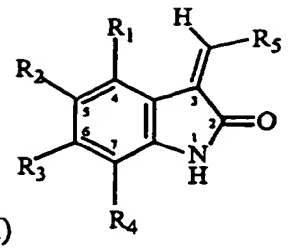
- The Examiner has maintained the rejection of claims 1-11, 15-18, 23-24 and 28 under 35 U.S.C. §103(a) as being unpatentable over Ullrich in view of Hirth in view of Mandriota in view of Tang and further in view of Fingl and Woodbury.

- The Examiner has maintained the rejection of claims 1-11, 15-18, 23-24 and 28-31 under 35 U.S.C. §103(a) as being unpatentable over Ullrich in view of Hirth in view of Mandriota in view of Tang and further in view of Fingl and Woodbury.

In this response, Applicants have amended claim 1 to incorporate the subject matter of claims 4, 5 and 7. In view of these amendments, Applicants respectfully traverse the Examiner's rejections for the reasons set forth below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143.

With particular regard to the rejection based on the combination of Ullrich in view of Hirth in view of Mandriota and further in view of Fingl and Woodbury, Applicants submit that none of these references, taken either individually or in combination, teach or properly suggest "an indolinone compound, having the structure set forth in formula I:



(I)

wherein (i) R1, R2, R3, and R4 are selected from the group consisting of hydrogen, trihalomethyl, hydroxyl, amine, thioether, cyano, alkoxy, alkyl, amino, bromo, fluoro, chloro, iodo, mercapto, thio, cyanoamido, alkylthio, aryl, heteroaryl, carboxyl, ester, oxo, alkoxycarbonyl, alkenyl, alkoxy, nitro, alkoxyl, and amido moieties; and (ii) R5, is an optionally substituted aryl or heteroaryl cyclic moiety; or a pharmaceutically acceptable salt, ester, amide, prodrug, isomer, or metabolite thereof" as recited in amended claim 1. Accordingly, Applicants submit that this combination of references cannot render the presently claimed invention obvious within the meaning of 35 U.S.C. §103 and that this rejection should be withdrawn.

In addition, with regard to each of the rejections set forth in the Office Action, the Examiner has failed to establish either (1) a proper motivation to combine the references or (2) a reasonable expectation of success. Specifically, Applicants submit that the Examiner has failed to establish a proper motivation to combine either of the two primary references, Ullrich and Tang, which each relate to Flk-1 and VEGF with Mandriota which relates to u-PA.

With specific regard to the rejections based on Ullrich, Applicants note that Ullrich fails to teach or fairly suggest monitoring markers, and, further, Ullrich fails to teach or fairly suggest monitoring of u-PA. While Mandriota discloses that u-PA increases with VEGF, this reference fails to disclose a method of determining an efficacious does of a compound administered to a subject for the purpose of modulating angiogenesis comprising monitoring u-PA. As the other cited references fail to cure these deficiencies, Applicants submit that none of the cited references, taken either individually or in combination, teach or properly suggest the inventions set forth in pending claim 1.

On page 2 of the Advisory Action, the Examiner contends, with regard to all of the obviousness rejections, (1) that a nexus between known markers and u-PA has been provided and (2) that clear motivation has been provided "for the reasons previously set forth". However, a review of both the Final Office Action and the Advisory action reveals neither a nexus between Mandriota and the other references nor a clear motivation for combining Mandriota with the other references. At best, the Examiner, using Applicants disclosure as a blueprint, appears to have selectively chosen bits and pieces of the prior art that were otherwise unrelated to arrive at the presently claimed invention. It is well settled that the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. MPEP §2141.

If an independent claim is nonobvious under §103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See MPEP 2143.03. Thus, Applicants submit that claims 2-3, 6, 8-11, 15-18, 23, 24 and 28-31, which depend directly or indirectly independent claim 1, are also non-obvious.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that all of the pending claims are now in condition for allowance. An early notice to this effect is earnestly solicited. If there are any questions regarding the application, the Examiner is invited to contact the undersigned at the number below.

Respectfully submitted,

Date April 21, 2003

By _____
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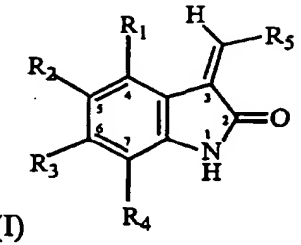
MARKED UP VERSION SHOWING CHANGES MADE

Below are the marked up amended claim(s):

1. (Twice Amended) A method of determining an efficacious dose of a compound administered to a subject for the purpose of modulating angiogenesis, comprising the steps of:

(a) administering the compound to a patient, **wherein the compound is a receptor antagonist that inhibits a receptor involved in angiogenesis and wherein the compound is an indolinone compound, having the structure set forth in formula I:**



(I)

wherein

(i) R1, R2, R3, and R4 are selected from the group consisting of hydrogen, trihalomethyl, hydroxyl, amine, thioether, cyano, alkoxy, alkyl, amino, bromo, fluoro, chloro, iodo, mercapto, thio, cyanoamido, alkylthio, aryl, heteroaryl, carboxyl, ester, oxo, alkoxycarbonyl, alkenyl, alkoxy, nitro, alkoxyl, and amido moieties; and

(ii) R5, is an optionally substituted aryl or heteroaryl cyclic moiety;

or a pharmaceutically acceptable salt, ester, amide, prodrug, isomer, or metabolite thereof;

(b) monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL8, and t-PA;

(c) constructing a standard curve; and

(d) determining the efficacious dose based on the standard curve.